

Fixed combination of atorvastatin/perindopril — modern prevention of cardiovascular events

Preparat złożony atorwastatyna/perindopril — nowoczesna prewencja zdarzeń sercowo-naczyniowych

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Abstract

Cardiovascular diseases are the leading cause of death in Poland. The most common cardiovascular risk factors are dyslipidemia and hypertension. Unfortunately, the percentage of patients with well-controlled dyslipidemia and hypertension remains very low. This is mainly due to insufficient statin therapy. Perindopril and atorvastatin are substances with a documented efficacy in reducing the incidence of cardiovascular events. The use of these drugs in one capsule can cause a significant increase in the percentage of patients properly treated and reaching the target values of blood pressure and LDL-cholesterol.

Key words: hypertension, hypercholesterolemia, perindopril, atorvastatin, combined therapy

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Introduction

Cardiovascular diseases remain the leading cause of death in Europe [1, 2]. In the Polish population, according to the results of the NATPOL study [3], dyslipidemia and hypertension are the two most common cardiovascular risk factors. Dyslipidemia occurs in 18 million Poles, and 10.5 million adult Poles suffer from hypertension. About 6.5 million Poles have hypertension and dyslipidemia [3] (Figure 1). A steady increase in the number of patients with hypertension and dyslipidemia is forecast [4].

In the observational POSTER study, conducted among 42,338 patients who were under outpatient medical care with hypertension, 77.8% of patients had lipid profile disorders and 68.3% had abdominal obesity. Over 25% of respondents smoked tobacco [5].

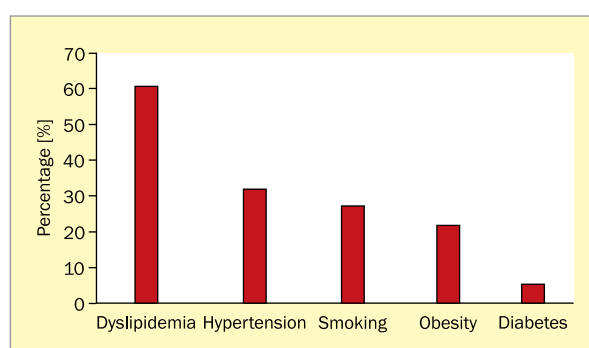


Figure 1. Prevalence of cardiovascular risk factors according to data from the NATPOL 2011 study (based on [3])

It is estimated that dyslipidemia also occurs in half of the hypertensive patients in the general population, which

is why the term 'lipitension' has recently become established in the literature, suggesting firstly the coexistence of these diseases, and secondly their synergistic adverse effect on patient prognosis [6].

Why is the simultaneous control of hypertension and hypercholesterolemia so important?

The coexistence of hypertension and dyslipidemia potentiates cardiovascular risk. In both the joint guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) published in 2018, and in the 2019 guidelines of the Polish Society of Hypertension (PTNT, *Polskie Towarzystwo Nadciśnienia Tętniczego*), risk assessment is recommended of the cardiovascular system in patients with hypertension [7, 8]. According to the assessment of global cardiovascular risk based on the Framingham model in a patient with hypertension, the presence of dyslipidemia as a single cardiovascular risk factor qualifies the patient as being at least at moderate global risk (Table 1). Hypertension and dyslipidemia are well recognised as risk factors for vascular diseases, which is why patients with these factors are often burdened with very high global risk [8].

Proper control of hypertension and dyslipidemia is important because of the possibility of reducing the risk of death and the incidence of cardiovascular disease. It is estimated that in Poland the percentage of premature mortality, i.e. deaths of people aged 25–64 due to cardiovascular diseases, is more than two times higher than in other European Union countries [9].

Which patients have common indications for the use of an angiotensin-converting enzyme inhibitor and a statin?

Angiotensin-converting enzymes (ACE) and statins have been widely used in many patients for many years. In light of current guidelines, the combined use of an ACE inhibitor and a statin is recommended for patients:

- with hypertension and dyslipidemia;
- hypertension with high and very high cardiovascular risk;
- hypertension and diabetes;
- stable coronary artery disease with hypertension;
- acute coronary syndrome — treated both conservatively and invasively.

The results of numerous studies on the use of statins in primary and secondary prevention, in which a significant percentage of the studied population were hypertensive patients, indicate that the optimal reduction in the global risk of cardiovascular complications is obtained by the simultaneous reduction of blood pressure and low-density lipoprotein (LDL) cholesterol [8]. According to the Pol-SCORE scale, every man with hypertension aged over 55 and every woman over 65 is at high or very high risk of cardiovascular death, so they should take a statin even though they have a normal lipid profile. The administration of an ACE inhibitor should be considered for patients with chronic coronary syndrome, especially with concomitant hypertension, left ventricular ejection fraction below 40%, diabetes or chronic kidney disease. Patients with documented coronary artery disease are at high risk and should be treated with statins [10].

Table 1. Assessment of global risk in a patient with hypertension modelled on the Framingham model (based on [8])

Stage of hypertension		BP [mm Hg]			
		High correct BP SBP 130–139 DBP 85–89	Hypertension 1 st degree SBP 140–159 DBP 90–99	Hypertension 2 nd degree SBP 160–179 DBP 100–109	Hypertension 3 rd degree SBP ≥ 180 DBP ≥ 110
Stage 1	No risk factors	Low	Low	Moderate	High
	1–2 risk factors	Low	Moderate	Moderate/ /high	High
	≥ 3 risk factors	Low/ /moderate	Moderate/ /high	High	High
Stage 2	Organ complications, diabetes without compli- cations, grade 3 CKD	Moderate/ /high	High	High	Very high
Stage 3	Overt cardiovascular disease, complicated diabetes, CKD ≥ grade 4	Very high	Very high	Very high	Very high

BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; CKD — chronic kidney disease

In which patient groups are ACE inhibitors preferred over sartans?

According to the PTNT guidelines of 2019, ACE inhibitors are antihypertensive drugs of the first choice in patients with:

- heart failure;
- chronic coronary syndrome;
- atherosclerosis of the lower extremities;
- metabolic syndrome;
- diabetes;
- hyperuricemia/gout;
- potency disorders;
- chronic kidney disease;
- albuminuria;
- renal failure [8].

ACE inhibitors are not drugs with the same properties; they differ within the group. That is why the authors of the PTNT guidelines from 2019 distinguished between some of them in specific indications. Perindopril, ramipril or zofenopril are preferred in patients with hypertension and chronic coronary syndrome. Perindopril and ramipril are preferred in patients with hypertension and diabetes or cardiovascular or metabolic complications [8].

In addition, in the recommended combination regimen for combined antihypertensive therapy, depending on the presence of comorbidities, ACE inhibitors are present in each recommended combination:

- ACE inhibitor and beta-blocker — in patients who have had a heart attack or heart failure;
- ACE inhibitor/sartan and thiazide/thiazide diuretic — in patients with diabetes, after a stroke, with renal dysfunction, in the elderly;
- ACE inhibitor/sartan and calcium antagonist — in patients with diabetes or with metabolic syndrome [8].

The strong position of ACE inhibitors in subsequent guidance documents has been strengthened thanks to the results of studies and meta-analyses confirming the hypotensive efficacy of the ACE inhibitor, but above all the reduction in the incidence of hard endpoints.

Van Vark et al. [11] analysed 158,998 patients from 20 clinical trials who had been randomised to treatment with a drug blocking the renin-angiotensin-aldosterone system (N = 71,401) or to a no-treatment control group (N = 87,597). Seven clinical studies concerned ACE inhibitors and 13 concerned sartans. There were significant differences in the subanalysis of the effect of ACE inhibitors and sartans on the reduction of overall and cardiovascular mortality. The use of ACE inhibitors was associated with a statistically significant ($p = 0.004$) reduction in the death rate by 10% and cardiovascular death by 12% ($p = 0.051$), while the use of sartans did not significantly affect total mortality [hazard ratio (HR) 0.99, $p = 0.683$] or cardiovascular mortality (HR 0.96, $p = 0.143$). The difference in the effect of both drug

groups on total mortality in favour of ACE inhibitors was statistically significant ($p = 0.036$).

Similar conclusions are included in the next meta-analysis, by Savarese et al. [12], based on the analysis of data of 108,212 patients at high cardiovascular risk (excluding patients with heart failure) treated with ACE inhibitors or sartans. On the other hand, in a Korean registry including 12,481 patients after myocardial infarction, Choi et al. [13] showed a reduction in cardiovascular and general mortality in a one-year follow-up in patients treated with ACE inhibitors compared to patients treated with sartans.

Brugets et al. [14] evaluated the incidence of end events in hypertensive patients treated with ACE inhibitors or sartans. Their meta-analysis of 18 studies showed that patients treated with ACE inhibitors were less likely to have fatalities due to general and cardiovascular causes, as well as heart attacks.

What is the synergistic effect of atorvastatin and perindopril on cardiovascular protection?

Perindopril is an ACE inhibitor with high antihypertensive effectiveness and many beneficial properties that result from its pleiotropic effect. It has been shown to be effective in the prevention of premature death and cardiovascular complications in many clinical studies: ASCOT (Anglo-Scandinavian Cardiac Outcomes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and DiamicroN MR Controlled Evaluation), and HYVET (Hypertension in the Very Elderly Trial) [15–17].

Perindopril has a higher binding specificity to the tissue ACE fraction ('tissue' ACE inhibitor) than traditional hydrophilic ACE inhibitors, such as enalapril and captopril, which bind strongly to the enzyme plasma fraction ('plasma' ACE inhibitors). There are no clinically significant differences between the two groups (i.e. 'plasma' vs. 'tissue') of ACE inhibitors in reducing cardiovascular morbidity and mortality, but drugs from the 'tissue' ACE inhibitor group are characterised by more favourable pharmacokinetic properties, mainly in terms of the length of the effective hypotensive period, i.e. the T/P (through-to-peak ratio) ratio, as well as a greater ability to selectively bind bradykinin in ACE compared to 'plasma' ACE inhibitors, and this may be of clinical significance [18]. Ceconi et al. [18] showed that among many active metabolites of ACE inhibitors, of which enalaprilat, perindoprilat, quinaprilat, ramiprilat andtrandolaprilat were studied, perindoprilat showed the greatest ability to selectively bind bradykinin. This specificity is measured by the selective bradykinin/angiotensin I binding index, which is 1.44 for perindopril, and for other tissue ACE inhibitors it also exceeds 1.0 (ramipril — 1.16 andtrandolapril — 1.08, respectively), while the lowest 1.0 plasma (balance of binding to bradykinin and angiotensin I) for the

plasma ACE inhibitor is enalapril. Moreover, comparing the equivalent doses and binding capacity of angiotensin I, it has been shown that perindoprilat has an almost 50% greater bradykinin binding capacity than enalaprilate [18]. This biochemical property of perindopril may explain its beneficial effect in the prevention of cardiovascular events. The ACE is also responsible for the breakdown of bradykinin, whose concentration in the blood increases during treatment with ACE inhibitors. Increased bradykinin levels have potentially beneficial vasodilatory, cardioprotective and anti-hypertrophic effects. The multicentre COMPLIOR study showed that long-term administration of perindopril increased the elasticity and compliance of the aorta [19]. An important pleiotropic effect of perindopril is a protective effect on endothelial function, as demonstrated by a group of researchers in the PERFECT study (PERindopril-Function of the Endothelium in Coronary artery disease Trial), which is a subanalysis of the EUROPA study [20]. This study evaluated the effect of long-term perindopril 8 mg/day on the rate of flow-mediated vasodilatation (FMD), an exponent of endothelial function. In a group of 333 patients, a beneficial, although not statistically significant, effect of perindopril on improving endothelial function, measured as an increase in FMD after 36 months of therapy, was demonstrated. The properties of perindopril are given in Table 2 [21].

The effect of statins is both a lipid-lowering effect and an additional non-lipolipemic effect resulting from the pleiotropic effect of statins, which is a consequence of:

- inhibition of fatty acid metabolism;
- inhibiting the inflammatory reaction;
- anticoagulant effect;
- a beneficial effect on the synthesis of nitric oxide, which improves the function of vascular endothelium;
- stabilisation of atherosclerotic plaque.

These mechanisms of pleiotropic action of statins are particularly important in patients with complications

of hypertension, and statins in this group of patients significantly improve prognosis. Taking into account the LDL-cholesterol target values to be achieved in patients with hypertension and dyslipidemia, it is advisable to use high-dose statins such as atorvastatin or rosuvastatin in this group of patients.

The synergistic effect of perindopril and atorvastatin may be due to their antiatherosclerotic effect. Both drugs stabilise atherosclerotic plaque by inhibiting endothelial dysfunction, oxidation of LDL-cholesterol and smooth muscle proliferation.

In the lipid arm of the ASCOT study, 10,305 patients with total cholesterol below 250 mg/dL were randomised to receive either a placebo or atorvastatin. Compared to the placebo, atorvastatin reduced the number of non-fatal or fatal coronary heart attacks by 53% [HR 0.47, 95% confidence interval (CI) 0.32–0.69, $p < 0.0001$] among patients assigned to therapy based on perindopril and amlodipine, while in the group of patients treated with atenolol and thiazide the reduction in the incidence of the endpoint was only 16% (HR 0.84; 95% CI 0.60–1.17, $p = 0.30$), which may result from the special synergy of atherosclerosis, atorvastatin, perindopril and amlodipine (Figure 2) [22]. In addition, based on a 16-year observation of patients from the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm) study, Gupta et al. [23] showed that adding statins to antihypertensive drugs compared to a placebo reduced cardiovascular mortality by 15%.

How to improve compliance for a patient being treated for hypertension and dyslipidemia?

According to data from the World Health Organisation (WHO), almost half of patients do not follow the treatment regimen recommended by their doctors. This phenomenon is particularly common among people with chronic, mild or asymptomatic diseases, requiring long-term treatment and the use of several medications. These conditions include hypertension and dyslipidemia.

In many patients, hypertension and lipid disorders are not treated efficiently. According to the NATPOL 2011 study, hypercholesterolemia in Poland is successfully treated in only 11% of patients, and hypertension in 26% [24]. While the effectiveness of hypertension treatment in Poland has been steadily increasing, from 12% to 26% according to the NATPOL study from 2002 and 2011, the effectiveness of dyslipidemia treatment remains very low. This is due to both the lack of patient cooperation in the use of lipid-lowering therapy, and the prescription of low doses of statins.

The results of the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) study, in which secondary prevention was assessed in people with coronary artery disease (after myocardial

Table 2. Properties of perindopril compared to other angiotensin-converting enzyme inhibitors (based on [21])

Stronger inhibition of the angiotensin-converting enzyme in blood and target tissues
Greater selectivity in relation to target organs
Greater selectivity for bradykinin binding
Greater efficiency in inhibiting endothelial cell apoptosis
Greater increase in the content and activity of nitric oxide synthase in aortic endothelium and cardiomyocytes
Greater antioxidant, anti-inflammatory, anticoagulant and profibrinolytic effect
Improvement of the coronary reserve in chronic coronary syndrome

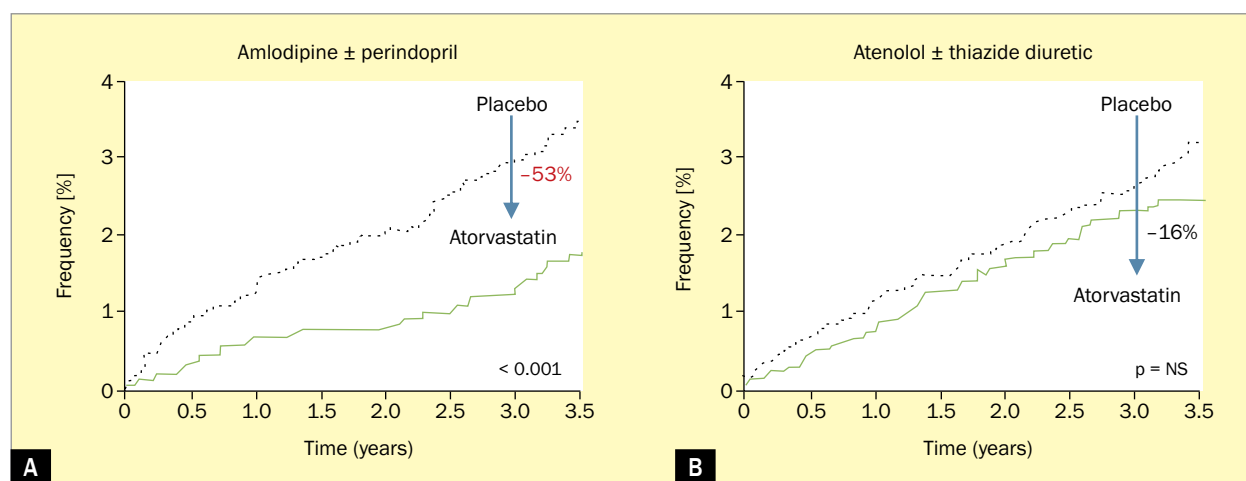


Figure 2A, B. The incidence of non-fatal myocardial infarction or death due to coronary artery disease in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm) study (based on [22]); NS – not statistically significant

infarction, percutaneous coronary intervention, and coronary artery bypass grafting, revealed that over 80% patients had elevated cholesterol values. Despite the increase in the frequency of lipid-lowering therapy (up to 85%) in subsequent editions of the study, the effectiveness of achieving the target concentration of LDL-cholesterol was low and amounted to 30% [25].

In the POL-FOKUS study, it was shown that seven out of 10 patients with hypertension receive simultaneously antihypertensive drugs and a statin. Only four out of these seven achieved satisfactory control of LDL-cholesterol [26]. The low rate of statin use among Polish patients in almost every age group is also demonstrated by data from the National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*). In the methodology of the study, medication possession ratio (MPR) was used in the assessment of adherence – an indicator estimated on the basis of issued prescriptions and dispensed prescriptions. An MPR of 100% means that the number of tablets the patient has is equal to the number of days from the implementation of one prescription to the implementation of the next prescription (i.e. the patient bought a 90-tablet pack of statins, and bought another pack after 90 days). The lower the MPR rate, the less frequently the patient completed prescriptions and had fewer medications than the number of days between subsequent prescriptions. The study by Wiśniowska and Skowron [27] showed that the average MPR value was 55.8% (52–63% in different age group ranges). Compliance has not reached the minimum level guaranteeing clinical benefits (80%) in any age group. An appropriate level of compliance with medical recommendations regarding statin treatment was found in 27.2% of respondents. Most people in all age groups discontinued statin treatment during the first 30 days of treatment [27].

In order to improve the quality of dyslipidemia treatment, it is necessary to simplify therapy, especially in patients with concomitant hypertension. It has been shown that the highest probability of continuing therapy was associated with the inclusion of several drugs at the same time or in a short period of time. It was observed that patients starting antihypertensive and lipid-lowering therapy on the same day, or at most within one month, adhered more closely to medical recommendations by 34% [28], while patients in whom lipid-lowering and antihypertensive drugs were introduced across a greater interval of time were less likely to follow the therapeutic regimen [29].

Chapman et al. [28], in an American patient population, showed that the adherence of patients treated for hypertension and dyslipidemia significantly deteriorated after the first six months of therapy and was only 35.8%. The authors of this report emphasised that reducing the number of tablets taken by the patient when starting therapy for hypertension and dyslipidemia may improve patient adherence.

One of the most effective methods to increase the effectiveness of antihypertensive and lipid-lowering treatment is to reduce the number of tablets ingested. A simplification of the treatment regimen, in numerous studies and meta-analyses, has been associated with a significant improvement in compliance with medical recommendations, regardless of the group of drugs used. Significant differences have been observed between patients using drugs once daily compared to their use more often. It has also been observed that fewer doses of medication taken by patients during the day were associated not only with improved collaboration, but also with increased treatment efficacy.

To sum up, using atorvastatin/perindopril in one capsule can result in greater treatment effectiveness and

easier therapeutic goal achievement, both in terms of lowering blood pressure and affecting the result of the lipiogram. Good blood pressure control may be an indicator that the patient is not taking only a hypotensive drug, but also an additional statin, in one capsule.

Can atorvastatin be given in the morning?

It is generally accepted that lipid-lowering drugs should be used in the evening, due to the peak of endogenous cholesterol synthesis in the liver at night. This rule applies to older generation statins, i.e. pravastatin, lovastatin and simvastatin, which have a short half-life (approx. 6 h). Conversely, atorvastatin and rosuvastatin, the most commonly used statins, have longer half-lives and can also be used in the morning. In addition, atorvastatin metabolites also inhibit cholesterol production.

Awad et al. [30] compared the results of lipidograms in patients treated with statins administered in the morning and in the evening in a meta-analysis involving 1,034 patients. In patients treated with long-acting statins, no differences in lipidogram parameters were observed between the groups of patients receiving morning and evening statins.

The recommendation of using a statin in the morning significantly increases the proportion of patients who regularly take medicines.

Perindopril with atorvastatin in one capsule — will this drug be used in my daily practice?

1. This drug is a combination of effective substances with proven action in the prevention of cardiovascular events

Perindopril is a potent long-acting hypotensive agent, and atorvastatin is a potent statin. Both drugs are characterised by unique properties and pleiotropic effects. The synergy of their antiatherosclerotic activity has been demonstrated in relation to the reduction in endpoint frequency in numerous studies (e.g. EUROPA, ASCOT-LLA).

Table 3. Available doses of the fixed combination drug of atorvastatin/perindopril (based on [31])

Atorvastatin	Perindopril	
10 mg	5 mg	10 mg
20 mg	5 mg	10 mg
40 mg	5 mg	10 mg

2. A fixed combination drug helps to improve compliance with medical recommendations

In Poland, hypertension and especially dyslipidemia are under-treated. Only 11% of patients reach their LDL-cholesterol target. The lack of control of these two risk factors eliminates the clinical benefits of taking medication. The recommendation of combination therapy consisting of perindopril and atorvastatin may significantly increase the proportion of patients taking a statin regularly.

3. The fixed combination drug of atorvastatin and perindopril has indications in numerous groups of patients, and the wide dose range allows selection of therapy in many patients

The fixed combination drug consisting of perindopril and atorvastatin can be used in patients with hypertension and dyslipidemia, chronic coronary syndrome, but also after acute coronary syndromes and coronary revascularisation. The wide range of six practical doses allows for individualised treatment of both hypertension and dyslipidemia in most patients (Table 3) [31].

It is worth remembering that if a greater reduction of blood pressure is needed, the combination drug atorvastatin/perindopril/amlodipine is available on the Polish market, which makes it possible to continue the treatment with the fixed combination drug.

Conflict of interests

The article was prepared with financial support from Servier Polska Sp. z o. o.

Streszczenie

Choroby układu sercowo-naczyniowego są główną przyczyną zgonów w Polsce, a najczęściej występujące czynniki ryzyka sercowo-naczyniowego to dyslipidemia i nadciśnienie tętnicze. Niestety odsetek chorych z dobrze kontrolowanymi dyslipidemią i nadciśnieniem tętniczym pozostaje bardzo niski. Wynika to głównie z niedostatecznej terapii statynami. Perindopril i atorwastatyna to substancje o udokumentowanym wpływie na ograniczenie częstości występowania zdarzeń sercowo-naczyniowych. Zastosowanie tych leków w jednej kapsułce może spowodować istotny wzrost odsetka chorych właściwie leczonych i osiągających docelowe wartości ciśnienia tętniczego i cholesterolu frakcji LDL.

Słowa kluczowe: nadciśnienie tętnicze, hipercholesterolemia, perindopril, atorwastatyna, leczenie skojarzone

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